

# Osteogenic Sarcoma of the Skull

## A Clinicopathologic Study of 19 Patients

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The authors studied 19 patients with well documented osteogenic sarcomas arising in the skull, which represent 1.6% of all osteogenic sarcomas registered during a 60-year period (1921-1981). Ten sarcomas were primary, *de novo* tumors. Nine others developed secondary osteogenic sarcomas; among these, six arose as a complication of Paget's disease, two followed irradiation, and one was associated with pre-existent fibrous dysplasia. The sarcomas arose in equal proportion in both sexes with the men being much older (mean age, 44 years) as compared to the women (mean age, 31 years). Patients with *de novo* osteogenic sarcomas were considerably younger than those with secondary lesions. Osteoblastic osteogenic sarcoma was by far the most common histologic variant in both the primary and the Paget's sarcomas. None of the patients with Paget's sarcoma lived longer than 1 year; the median survival here was 4 months. Patients with *de novo* osteogenic sarcomas fared much better and there are four long-term survivors (longer than 3 years) who are currently disease-free.

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THE DEVELOPMENT of a primary or secondary osteogenic sarcoma in the cranial vault is a well recognized, albeit extremely infrequent occurrence, with an ominous clinical outcome.<sup>1-21</sup> The habitually fatal consequence of sarcomas arising in association with Paget's disease of the skull, as is the case so often at this anatomic location, represents one of the most feared type of sarcoma known.<sup>22-27</sup> A comprehensive re-evaluation of all osteogenic sarcomas at Memorial Sloan-Kettering Cancer Center gave us a rare opportunity to study the manifold clinical and pathologic manifestations of these neoplasms, compare those which arose anew (*de novo*) from previously normal calvaria to examples which followed irradiation or Paget's disease.<sup>28-32</sup> This analysis updates the study by Caron et al. and extends the review of the surgical experience of Thompson and his associates which included five cases from this Cancer Center.<sup>33,34</sup>

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### Materials and Methods

We have reviewed the clinical records, roentgenograms, and pathologic material of all patients diagnosed and treated at Memorial Hospital for Cancer and Allied Diseases between 1921 and 1981, in whom the diagnosis of osteogenic sarcoma was registered. Of those cases reviewed, more than 1200 were found to have adequate histologic, radiographic, and clinical documentation available to definitely warrant additional detailed evaluation. In 19 patients, the sarcomas arose in the skull. This study includes only those cases in which the osteogenic sarcomas were of skeletal origin and the diagnosis could be authenticated by microscopic examination.

Osteogenic sarcoma was considered to be a tumor in which the malignant spindle cell stroma directly formed osteoid or primitive bone.<sup>35</sup> No exceptions were made, and no sarcomas were included in this study in which these basic microscopic features were not met: thus, fibrosarcomas, malignant fibrous histiocytomas with or without "reactive ossification," malignant giant cell tumors, or chondrosarcomas with metaplastic or endochondral ossification were eliminated from further analysis. Similarly to osteogenic sarcomas at other sites these tumors were histologically subclassified into chondrosarcomatous, fibrosarcomatous, fibrohistiocytomatous, osteoblastic, small cell and telangiectatic types. Additionally, a special category was created for those cases in

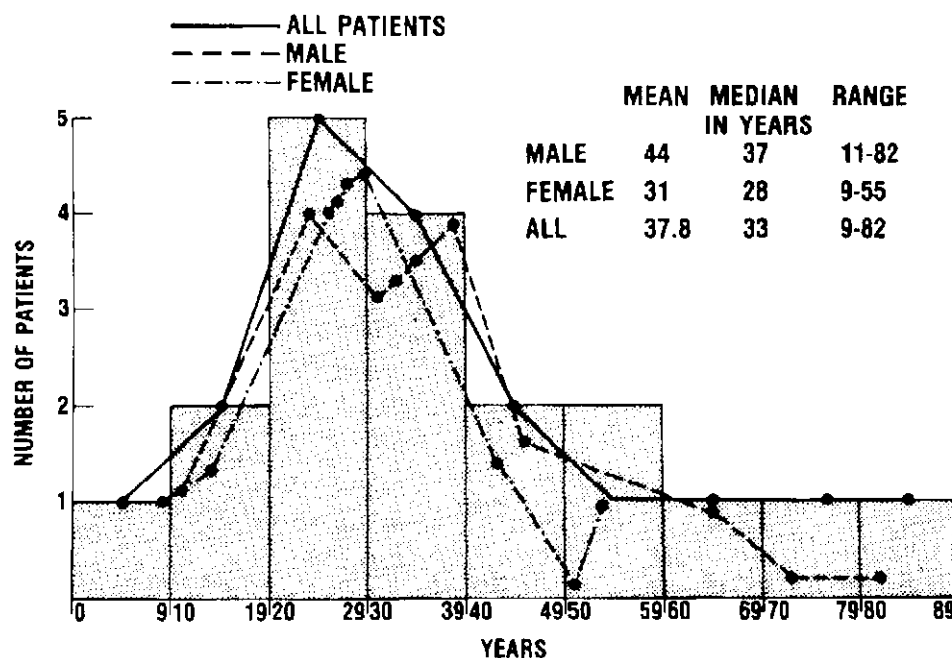


FIG. 1. Age and sex distribution in ten males and nine females with osteogenic sarcoma of the skull. The males are considerably older.

which the histologic study failed to show a predominant morphologic growth pattern, designated as the mixed pattern.

Regular annual follow-up was conducted on all patients included in this study and forms the basis of the survival analyses to be discussed in a subsequent section of this report.<sup>36,37</sup>

### Results

There were more than 1200 histologically verified osteogenic sarcoma patients diagnosed and treated at Memorial Hospital for Cancer and Allied Diseases during a 60-year period (1921-1981), and 19 (1.6%) had tumors which arose in the skull. The first patient was seen in 1943.

Among the 19 patients with osteogenic sarcomas of the skull, ten were primary *de novo* tumors and nine developed as secondary sarcomas either superimposed on Paget's disease of bone (6 cases), or in two as a complication of previous irradiation or in one, associated with fibrous dysplasia. In one patient the radiation was given as treatment for a nasopharyngeal carcinoma, in the other, for bilateral retinoblastoma.

The ages of the patients ranged from 9 to 82 years (mean, 38 years; median, 33 years) (Fig. 1). The mean age of patients with *de novo*, primary osteogenic sarcoma was 26 years, while those with secondary sarcomas averaged 48 years. There were 10 males with a mean age of 44 years (range, 11-82 years) and 9 females with a mean age of 31 years (range, 9-55 years). Three patients were 13 years or younger (16%).

Clinical symptoms and signs varied with the location, size of the tumor, as well as the rapidity of growth. Fifteen patients noticed a mass lesion on their skull and sought medical attention (Fig. 2). The remaining three presented with neurologic symptoms; one with headache, nausea, and vomiting suggesting an intracranial mass, another with facial palsy from tumor involving the temporal bone, and a third with proptosis. The duration of symptoms varied considerably from 2 months to 5 years (median, 6 months). The shortest duration was seen in patients with Paget's sarcoma, in whom the tumor mass grew rapidly over a few weeks. In the majority, the skull mass was painless at onset, thus delaying diagnosis. The longest time delay in diagnosis occurred in a patient with osteosarcoma secondary to fibrous dysplasia: he presented difficulty opening the jaws, and swelling of the temporal region. A limited biopsy was thought to represent fibrous dysplasia. The diagnosis of malignant transformation was established years later when he presented signs of intracranial invasion. In two patients with postradiation sarcomas, the second lesion was believed to represent recurrence of the original tumor. The 9-year-old child with bilateral retinoblastoma presented with a mass on the bregma, and the 28-year-old man, who received radiation therapy (4000 rad) along with Radon seed implants (11.9  $\mu$ C), presented with a skull mass along with proptosis and early papilledema.

On examination, the mass lesions were initially thought to be benign in six patients. The most frequent diagnosis was that of a "sebaceous cyst" or "osteoma"

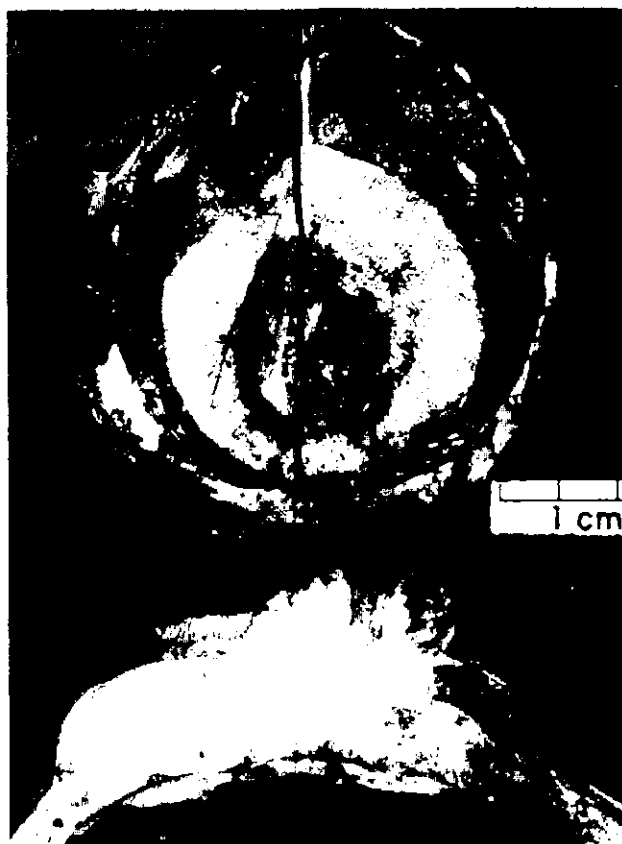


FIG. 2. Surgical specimen of a huge osteogenic sarcoma in the occipitoparietal region of the skull in a 28-year-old woman. The tumor extends mostly extracranially but definite involvement of the external and internal tables of the calvaria is noted.

of the skull. Even following radiologic evaluation, the radiologic findings were atypical enough to mimic benign entities in two others. Laboratory values of serum alkaline



FIG. 3. Typical sclerotic osteogenic sarcoma of the parietal region of the skull vault arising in a 48-year old man with polyostotic Paget's disease. Synchronous sarcomas arose in the right ilium and L5 vertebra.

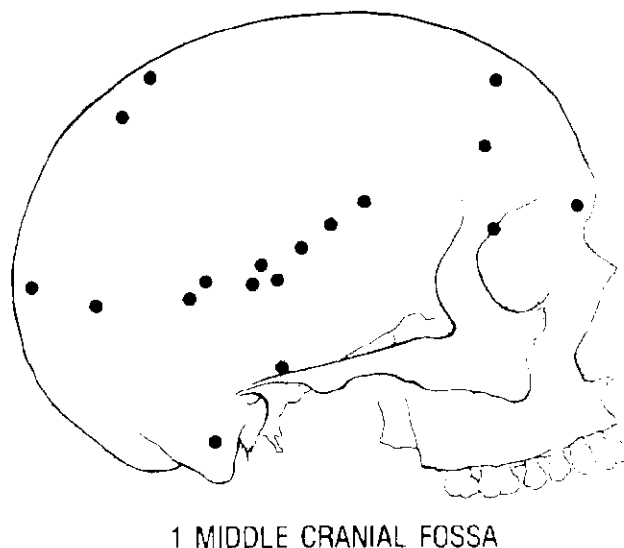


FIG. 4. Osteogenic sarcoma of the skull. Location of tumors in 19 patients.

phosphatase were available in 11 patients, and ranged from 117 to 386 International Units in the patients with *de novo* tumors, and values ranging from 500 to 2898 in patients with Paget's sarcoma. No elevation was noted in the two patients with radiation related sarcomas. The elevation of alkaline phosphatase was a nonspecific finding, and was more useful in determining results of therapy than in the original differential diagnosis.

The clinical size of the sarcoma varied from 3 to more than 8 cm in greatest diameter, and in eight patients the lesions measured more than 6 cm in greatest diameter. In eight patients sufficient details of the roentgen examination were available. Four of these had purely lytic, three sclerotic and one a permeative type of osseous destructive lesion (Fig. 3). In six the radiographic character of bone destruction was not mentioned.

The location of the 19 osteogenic sarcomas is depicted in Figure 4. Thirteen sarcomas occurred in the calvarium and six involved the skull base.

Histologic examination showed the osteogenic sarcomas to be fully malignant. In all but three cases, they could be divided into well recognized subtypes except those three cases in which no predominant histologic growth pattern (also called mixed histologic pattern) could readily be ascertained (Table 1). The most frequent histologic type by far was the osteoblastic variant (nine cases) constituting almost one half of all other cases (Fig. 5). Osteoblastic osteogenic sarcoma was also the most common histologic type associated with the six Paget's sarcomas (three cases) (Fig. 6). Next in frequency were those of the telangiectatic types (two cases) arising in Paget's disease and the remaining sarcoma showed no predominant histologic growth pattern.

TABLE 1. Histologic Variants in Osteogenic Sarcoma of the Skull

Type	No.	%
Osteoblastic	9	47.0
Chondrosarcomatous	3	16.0
Telangiectatic	2	10.5
Fibrohistiocytomatous	2	10.5
Mixed pattern	3	16.0
Total	19	100.0

In spite of the ready availability of the CT scans in six patients, the manifold and disparate presentations often precluded achieving accurate diagnoses except for identifying the presence, the exact site and size of the tumor. By this method of examination the diagnosis of meningioma and giant cell tumor of the skull base were made. Only in one instance was the sarcomatous conversion of a Paget's disease of the skull confidently predicted by CT scans (Figs. 7A and 7B).

In patients who had residual sarcoma following surgical excision, or subsequently developed clinical recurrence, radionuclide bone scans were of considerable use and found to be superior to a CT scan.

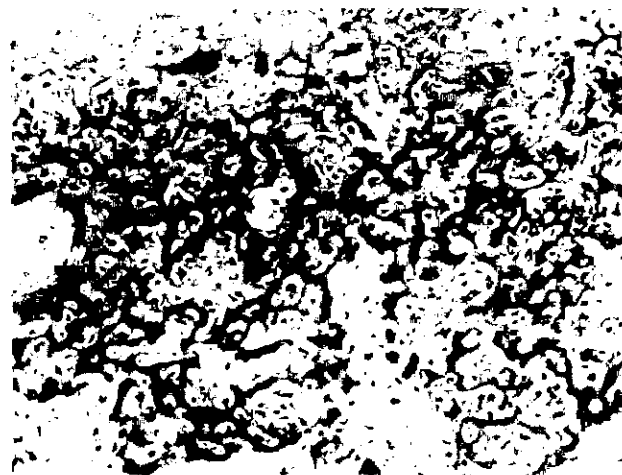


FIG. 5. Heavily ossified osteogenic sarcoma of the skull in which the sarcomatous stromal cells are surrounded by tumor osteoid and bone; a process referred as "normalization" (H & E  $\times 100$ ).

Cerebral angiography revealed in most instances the tumors to be fairly well vascularized and supplied by dural arterial vessels emanating from the external carotid

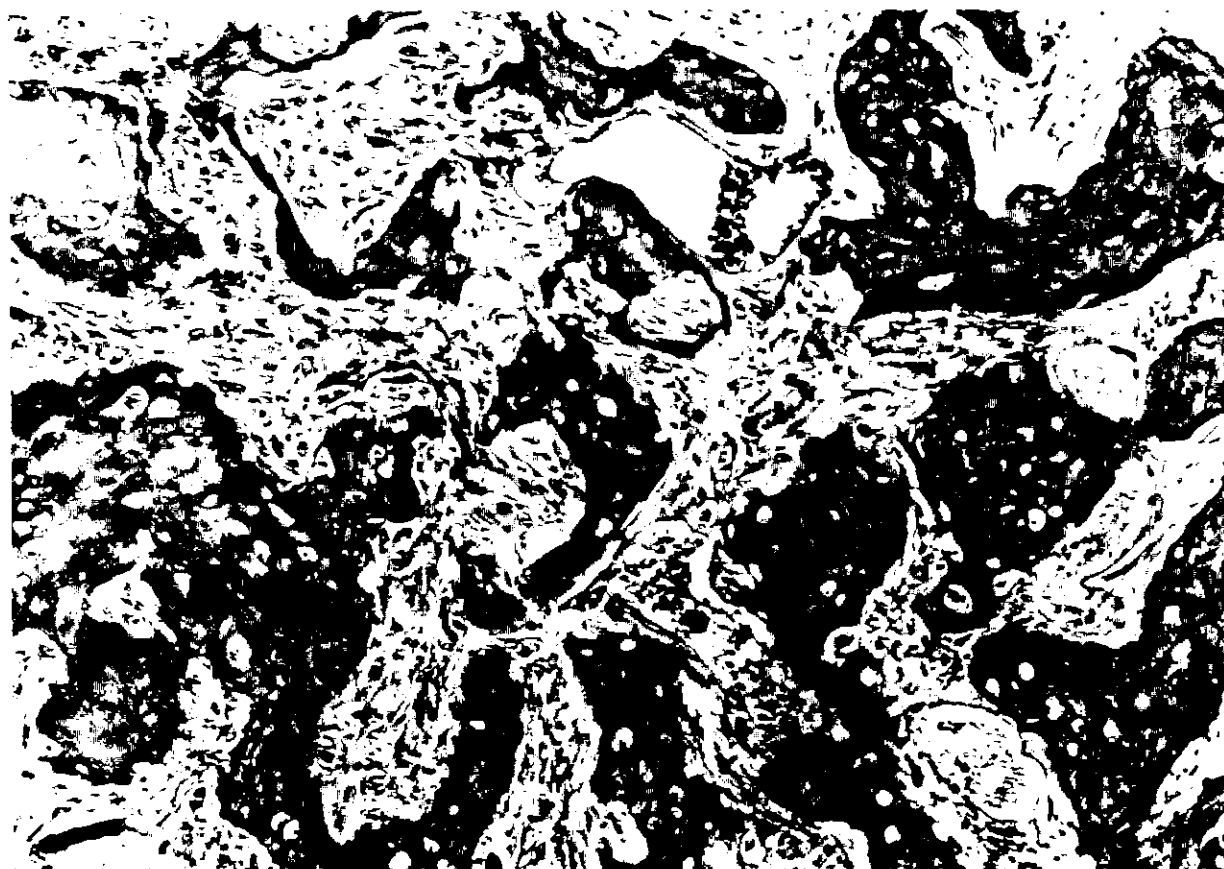
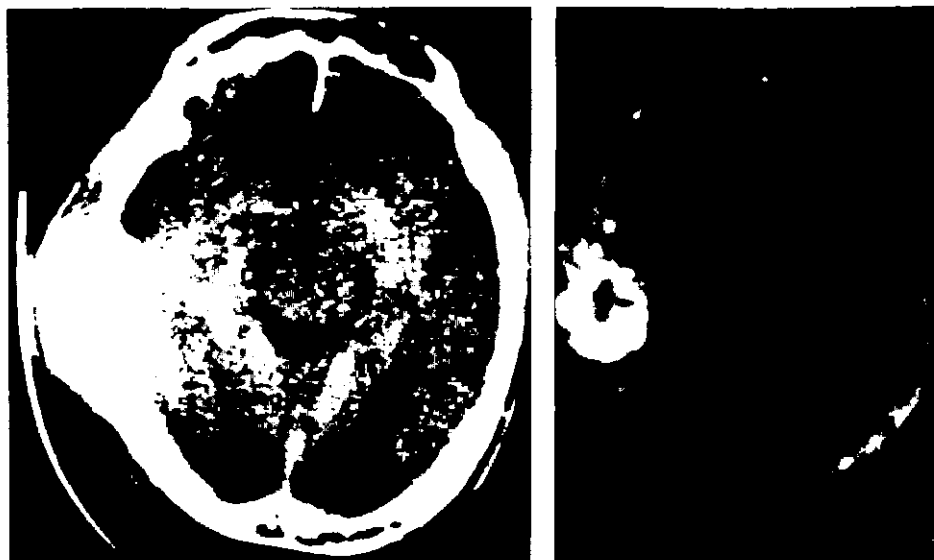


FIG. 6. Osteogenic sarcoma arising in Paget's disease of bone. Pagetic bony trabeculae surrounded by anaplastic osteoid producing fibroblastic sarcoma cells (H & E  $\times 100$ ).



FIGS. 7A AND 7B. (A, left) Axial CT scan with contrast in Paget's sarcoma of the temporoparietal region showing early intracranial invasion, as well as involvement of the scalp. This 73-year-old patient presented with a fluctuant scalp mass, that was thought to be a sebaceous cyst. (B, right) Axial CT scan with skeletal windows on patient above showing patchy, diffuse involvement with thickening of the calvarium that indicate severe Paget's disease.

arterial system. Tumor location over the superior sagittal or the transverse sinuses, especially in recurrent lesions, resulted in sinus occlusion; in this setting sinus invasion was strongly suspected on cerebral angiography.

### Treatment

Since this study spans over a 40 year period, there was considerable variation in therapeutic approaches. In the more recent cases, computerized tomography allowed more accurate assessment of tumor mass as well as degree of intracranial invasion, and thus encouraged a more aggressive surgical approach. Of the six patients with Paget's sarcoma, four underwent radiation therapy following aspiration biopsy and two had major surgical resections, with one postoperative death due to myocardial infarction. Examination at autopsy in this patient revealed no evidence of intracranial residual tumor but micrometastases in the lung. All patients with Paget's sarcoma died of their disease within 6 months. Their clinical course suggested early intracranial invasion and no response to external radiation therapy was noted. The two patients with postradiation sarcomas underwent subtotal resection followed by additional radiation therapy. One is a long-term survivor who underwent multiple resections. This patient finally died of a brain abscess 3 years later. The other patient showed no response to radiation therapy. In the ten patients with *de novo* sarcomas, treatment could be divided into three major groups, on the basis of surgical therapy. Two patients underwent biopsy only while seven had varying degrees of subtotal resection, and a complete resection was performed in one patient. Five patients received postoperative radiation therapy of doses ranging from 5000

to 6000 rads over a 5- to 6-week period using megavoltage equipment. The patient who underwent subtotal resection in addition to 6000 rad radiation therapy has lived 10 years, but has progressive neurologic symptoms probably due to radiation. Eight patients received chemotherapy. Initially dactinomycin and nitrogen mustard were used in three patients to supplement radiation therapy. Since 1972, the chemotherapeutic regimens were those developed by Rosen for the treatment of extremity osteosarcomas.<sup>38</sup> They included the use of high-dose methotrexate, BCD (bleomycin-Cytosan (vincristine)-dactinomycin), and Adriamycin (doxorubicin)-cisplatin drug combinations. Modifications in subsequent therapy were made following repeat resection of residual tumor, which allowed pathologic assessment of tumor response.

Overall results of treatment are shown in Figure 8. The patients with Paget's sarcoma had the poorest prognosis, with a median survival of 4 months, with no patient living to 1 year. Of the three other patients with secondary sarcomas, there was one long-term survivor of 3 years who developed osteogenic sarcoma following retinoblastoma therapy. Of the ten patients with *de novo* tumors, there are four long-term survivors (more than 3 years), and all are currently disease-free. Three of these patients have undergone both extended surgical resection, as well as intensive combination chemotherapy.

### Discussion

After the vertebral column, particularly the sacrum, the skull is the next most commonly involved bone by uncomplicated Paget's disease. The early lytic phase of this disease process is known at least since 1927 as

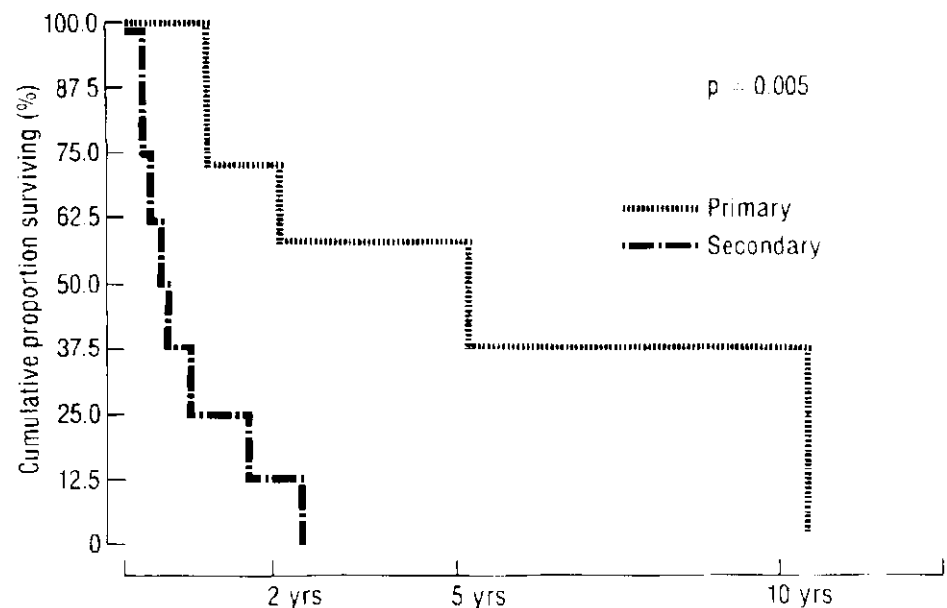


FIG. 8. Comparison of survival rates in patients with primary, *de novo* and secondary osteogenic sarcomas of the skull. The poor prognosis of Paget's sarcomas is clearly shown.

osteoporosis circumscripta of the skull.<sup>39</sup> While approximately 65% of patients with uncomplicated Paget's disease show skull involvement only 9% of Paget's sarcomas arise at this site.<sup>40-43</sup>

The majority of patients with osteosarcomas present with painless mass lesions and a complete radiologic evaluation is indicated. This should include both bone scan and computerized tomography. All those with Paget's disease should be closely followed by their primary physician, since malignant transformation (although rare) may be sudden. These patients should therefore be advised to seek medical attention if sudden enlargement with skull mass develops. All such masses in patients with Paget's disease should undergo biopsy. Since early micrometastases may already be present, we would favor the use of aggressive preoperative chemotherapy prior to definitive surgical resection in this group of patients.

Radiologists may play a pivotal role in evaluating suspicious radiolucencies of the skull in patients with stigmata of Paget's disease. Rarely, the patients' complaints are related to pagetic lesions other than those in the calvaria, and the skull involvement becomes obvious only by a thorough examination, primarily aimed at other sites. In other instances, which are the norm, the symptoms arise from the skull lesion primarily, and this in turn leads to the discovery of polyostotic involvement by Paget's disease. The strict radiologic separation of osteogenic sarcoma complicating Paget's disease and those showing only changes of uncomplicated disease without sarcoma may be difficult in some cases. The presence of a soft tissue mass in addition to the typical

thickening of the outer table of the cranial vault with loss of distinction between the tables and the diploë alternating with radiolucency and sclerosis are those of a sarcoma arising in Paget's disease of the skull.

The usually accepted radiographic features of osteogenic sarcoma arising anew from the skull are found wanting in the setting of a bone sarcoma complicating Paget's disease.<sup>41</sup> The panoply of periosteal alterations, osseous matrix production and bone destruction classically seen in *de novo* osteogenic sarcomas may not always have diagnostic relevance in Paget's sarcomas of the skull. Here the thickened cranial vault, the blurred cortical outlines accompanying the heavy bone sclerosis and bone destruction of the so-called "cotton wool" type in uncomplicated Paget's disease may disguise the usual changes associated with osteogenic sarcoma. On plain radiographic examination an early lytic destructive tumor of small size may readily be glossed over.<sup>43</sup> Tangential views, however, will greatly facilitate recognition of the true nature of a patchy radiolucency engrafted on a Paget's disease. Comparison of sequential radiographs are of considerable help. Techniques of CT scanning seem to provide the often needed refinement in positively identifying even the earliest irregularities in the cranial outlines and cortical deformities.<sup>41</sup> Important additional data concerning dural extension of tumor as well as brain involvement are readily obtainable from studying CT scans. Some studies indicate the value of a complete neuroradiological evaluation including selective angiography to delineate the best therapeutic strategy.<sup>41</sup>

In spite of reports to the contrary, Paget's sarcomas affecting the skull did not occur more frequently in

women than men in this study.<sup>44</sup> Osteogenic sarcoma arising in the skull, both the primary or the secondary type, is in general, a disease of the skeletally mature in contrast to those which affect the appendicular skeleton, where it is more likely to appear during the skeletal growth spurt. A similar relationship between age and the skeletal distribution pattern exists in canines and smaller animal breeds as well.<sup>45-50</sup> Older Boxer dogs are most frequently affected by osteogenic sarcomas of the skull, while the same site is practically never noted in St. Bernards and Great Danes, where the forelimbs are preferentially involved.

The early symptoms of calvarial osteogenic sarcomas are characterized by an intermittent neuralgic type of pain, quite severe, which may be experienced before the typical circumferential thickening of the skull of Paget's disease becomes obvious. A rapidly growing scalp mass often heralded the presence of a Paget's sarcoma. In more advanced stages of the sarcoma the deformity of the skull due to the tumor mass is quite noticeable. On incisional biopsy excessive bleeding may ensue due to the extreme vascularity of both surrounding pagetic bone and bone marrow as well as the osteogenic sarcoma. A needle biopsy here provided quick diagnosis without undue bleeding.

The roentgen appearances of osteogenic sarcoma of the cranium were variable and the purely lytic ones were slightly more common than the sclerotic or the combination of these two presentations. The predominantly lytic destructive lesions are almost totally those of an area of bony destruction. In the sclerosing types of sarcomas a great deal of tumor bone is produced and the plain radiographs show features of excessive bone formation, sometimes with a "sun-ray" or "hair on end" appearance. An intermixture of both sclerotic and lytic destructive areas is often featured. None of the osteogenic sarcomas seemed to arise in parosteal location, although this presentation may be occasionally seen in felines and canines.<sup>48,49</sup>

The treatment of osteogenic sarcoma arising in the skull has entered a protracted period of trial and profound challenge. The dominant issue here is simply whether the major current treatment advances and markedly improved prognosis, as are true with histologically similar lesions affecting the appendicular skeleton, can readily be translated into the cranial site as well. Can aggressive preoperative chemotherapy turn around the bleak survival prospects of patients with calvarial osteogenic sarcoma? Is the full range of the previously unavailable but currently almost commonplace therapeutic and diagnostic pursuits now on the verge of resounding success in obtaining better all around survival results? The overall previous records of survival statistics are a sorry

catalogue of massive locally recurrent disease and ultimate failure; hopefully all this will be changed.

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